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LETTER TO THE EDITOR

Authors' Reply to Kamel et al.: "Effect of Age and Renal Function on Idarucizumab Pharmacokinetics and Idarucizumab-Mediated Reversal of Dabigatran Anticoagulant Activity in a Randomized, Double-Blind, Crossover Phase Ib Study"

Stephan Glund[1] · Paul Reilly[2] · Joanne van Ryn[3] · Joachim Stangier[3]

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We thank Dr. Kamel and colleagues for their valuable comments [1] and would like to provide the following response to the questions raised.

The unbound dabigatran concentration reflects the level of active dabigatran in the blood. Administration of idarucizumab 5 g to volunteers of various age groups and with different degrees of renal impairment reduced unbound dabigatran concentrations to below the lower limit of quantitation (LLOQ) (1 ng/mL). Approximately 12–16 h post-idarucizumab administration, an increase in the concentrations of unbound dabigatran above the LLOQ was noted. Importantly, the underlying detection methodology is highly sensitive and, over the entire observation period, levels did not increase above the threshold for pharmacological activity. Consequently, coagulation time measurements also did not increase above their respective upper limits of normal, as illustrated for activated partial thromboplastin time in Table 1.

A 5 g dose of idarucizumab completely neutralizes dabigatran anticoagulation in almost all patients, as demonstrated by coagulation time measurements in dabigatran-treated patients receiving idarucizumab as emergency treatment [2]. Coagulation time measurements are frequently applied as routine measures in clinical emergency settings, and the results can provide important information supporting rational treatment decisions. In REVERSE AD (REVERSal Effects of idarucizumab in patients on Active Dabigatran), patients' coagulation times were determined up to 24 h after idarucizumab administration [2]. In this timeframe most clinical emergencies are expected to resolve. A re-occurrence of dabigatran anticoagulation was noted in some patients, mostly 12–24 h after idarucizumab administration [2]. Importantly, almost none of these patients were bleeding, suggesting that for these patients the re-elevation was not clinically relevant. However, as pointed out by Dr. Kamel and colleagues [1], there are certain clinical situations in which a re-occurrence of the anticoagulant effect of dabigatran might be harmful. Consequently, a second dose of idarucizumab was allowed in the RE-VERSE AD clinical trial; the respective data will be available in the final publication when the trial is complete. Consideration of an additional dose is also proposed in the idarucizumab label. The criteria for the additional dose focus on both the clinical condition of the patient as well as the coagulation status:

- recurrence of clinically relevant bleeding together with prolonged clotting times; or
- patients require a second emergency surgery/urgent procedure and have prolonged clotting times [3].

Dr. Kamel and colleagues further expressed interest in the non-renal contribution to idarucizumab elimination [1]. As this involves unspecific catabolism in the body followed by recycling of amino acids, it is not feasible to conduct

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✉ Stephan Glund
stephan.glund@boehringer-ingelheim.com

[1] Translational Medicine and Clinical Pharmacology, Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Straße 65, 88397 Biberach an der Riss, Germany

[2] Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA

[3] Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany

Table 1 Activated partial thromboplastin time (s) [mean (standard deviation)] values obtained 24–120 h after administration of idarucizumab 5 g in volunteers with mild or moderate renal impairment, pre-treated with dabigatran etexilate 150 mg twice daily; upper limit of normal = 39.8 s

Group	24 h	48 h	72 h	96 h	120 h
Mild RI	32.7 (0.85)	33.0 (0.96)	30.9 (1.58)	29.6 (3.02)	30.7 (2.09)
Moderate RI	33.3 (5.64)	32.7 (4.60)	31.1 (2.21)	30.8 (2.22)	31.3 (2.75)

RI renal impairment

appropriate mechanistic studies to address this question clinically. Based on our data in healthy volunteers [4, 5], we feel confident that in healthy subjects, renal clearance is the major pathway resulting in rapid elimination of the drug. However, there is a dependency of idarucizumab exposure on renal function, and under conditions of more severe renal damage non-renal elimination pathways may have increased relevance. We are currently analyzing our data on renal elimination and intend to publish the results.

Finally, the value for creatinine clearance (CL_{CR}) of volunteers with moderate renal impairment presented in our publication is correct. Volunteers with renal insufficiency were enrolled into the study based on their CL_{CR} value at the screening visit. The value presented in the table refers to the measurement at baseline, i.e., shortly before idarucizumab administration. Some of the levels measured at baseline were higher in the same individuals than those measured at screening, explaining the discrepancy.

Compliance with ethical standards

Conflicts of interest Stephan Glund, Joanne van Ryn, and Joachim Stangier are employees of Boehringer Ingelheim Pharma GmbH & Co. KG. Paul Reilly is an employee of Boehringer Ingelheim Pharmaceuticals, Inc.

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